

WE CLAIM:

1. A nucleic acid molecule comprising:
 - a) two or more target binding domains that target binding of the pre-trans-splicing molecule to a target pre-mRNA;
 - b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site and a 5' splice donor site;
 - c) spacer regions that separate the 3' splice region and the 5' splice donor site from the target binding domains; and
 - d) a nucleotide sequence to be *trans*-spliced to the target pre-mRNA; wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.
2. The nucleic acid molecule of claim 1 wherein the spacer regions separate the 3' splice region and the 5' splice donor site from the target binding domains.
3. The nucleic acid molecule of claim 1 wherein the nucleic acid molecule further comprises sequences encoding a translatable protein product.
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4. The nucleic acid molecule of claim 3 wherein the translatable protein product is a toxin.
5. The nucleic acid molecule of claim 1 wherein the nucleic acid molecule further comprises sequences containing a translational stop codon.
6. The molecule of claim 1 wherein the nucleotide sequence to be *trans*-spliced to the target pre-mRNA comprises nucleotide sequences encoding the cystic fibrosis trans-membrane conductance regulator.

7 The molecule of claim 6 wherein the nucleotide sequences encoding the cystic fibrosis trans-membrane conductance regulator comprise exon 10 of the cystic fibrosis trans-membrane regulator conductance gene.

8. A recombinant expression vector wherein said vector expresses a nucleotide sequence comprising:

- a) two or more target binding domains that target binding of the pre-*trans-splicing* molecule to a target pre-mRNA;
- b) a 3' splice region comprising a branchpoint, a pyrimidine tract and a 3' splice acceptor site and a 5' splice donor site;
- c) spacer regions that separate the 3' splice region and the 5' splice donor site from the target binding domains; and
- d) a nucleotide sequence to be *trans-spliced* to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell.

9. The molecule of claim 1 or 8 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the pre-*trans-splicing* molecule branch point, pyrimidine tract, 3' splice site or 5' splice site.

10. A cell comprising a nucleic acid molecule wherein said nucleic acid molecule comprises:

- a) two or more target binding domains that target binding of the pre-*trans-splicing* molecule to a target pre-mRNA;
- b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site and a 5' splice donor site;
- c) spacer regions that separate the 3' splice region and the 5' splice donor site from the target binding domains; and

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- d) a nucleotide sequence to be *trans*-spliced to the target pre-mRNA; wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.

11. The cell of claim 10 wherein the spacer regions of the nucleic acid molecule separate the 3' splice region and the 5' splice donor site from the target binding domains.

12. The cell of claim 10 wherein the nucleic acid molecule further comprises sequences encoding a translatable protein product.

13. The cell of claim 12 wherein translatable protein is a toxin.

14. The cell of claim 10 wherein the nucleic acid molecule further comprises a nucleotide sequence containing a translational stop codon.

15. The cell of claim 10 wherein the nucleotide sequence to be *trans*-spliced to the target pre-mRNA comprises nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator.

16. The cell of claim 10 wherein the nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator comprise exon 10 cystic fibrosis transmembrane conductance regulator gene.

17. A cell comprising a recombinant expression vector wherein said vector expresses a nucleotide sequence comprising:

- a) two or more target binding domains that target binding of the pre-*trans*-splicing molecule to a target pre-mRNA;
- b) a 3' splice region comprising a branchpoint, a pyrimidine tract and

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- c) a 3' splice acceptor site and a 5' splice donor site;
- d) spacer regions that separate the 3' splice region and the 5' splice donor site from the target binding domains; and
- d) a nucleotide sequence to be *trans*-spliced to the target pre-mRNA; wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.

18. A cell comprising the nucleic acid molecule of claim 1 or 8 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the pre-*trans*-splicing molecule branch point, pyrimidine tract, 3' splice site or 5' splice site.

19. A method of producing a chimeric mRNA molecule comprising contacting a pre-*trans*-splicing molecule with a target pre-mRNA under conditions in which a double *trans*-splicing reaction results in a portion of the pre-*trans*-splicing molecule being *trans*-spliced to a portion of the target pre-mRNA to form said chimeric mRNA.

20. The method of claim 19 wherein the pre-*trans*-splicing mRNA comprises nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator.

21. The method of claim 19 wherein the pre-*trans*-splicing mRNA comprises exon 10 cystic fibrosis transmembrane conductance regulator gene.

22. A method of providing a host cell with a chimeric mRNA molecule, said method comprising:

transferring a pre-*trans*-splicing molecule to a host cell expressing a target pre-mRNA wherein the pre-*trans*-splicing molecule binds to the target pre-mRNA under conditions in which a double *trans*-splicing reaction results in a portion of the pre-*trans*-splicing molecule being *trans*-spliced to a portion of the target pre-mRNA to form said chimeric mRNA.

23. The method of claim 20 wherein the host cell is a human cell.
24. The method of claim 20 wherein the pre-*trans*-splicing molecule comprises nucleotide sequences encoding a protein that is defective or lacking in the host cell.
25. The method of claim 22 wherein the pre-*trans*-splicing molecule comprises nucleotide sequences encoding a fragment of the cystic fibrosis trans-membrane regulator protein.
26. A pharmaceutical composition comprising the nucleic acid molecule of claim 1 and a pharmaceutically acceptable carrier.
27. A nucleic acid molecule comprising:
- a) one or more target binding domains that target binding of the pre-*trans*-splicing molecule to a target pre-mRNA;
 - b) a 5' splice donor site;
 - c) a spacer region that separates the 5' splice donor site from the target binding domain; and
 - d) a nucleotide sequence comprising the 5' end of a gene to be trans-spliced to the target pre-mRNA;
- wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.
28. The nucleic acid molecule of claim 27 wherein the nucleotide sequence to be the *trans*-spliced to the target pre-mRNA encodes a translatable protein product.
29. The nucleic acid molecule of claim 28 wherein the translatable protein product is a toxin.

30. The nucleic acid molecule of claim 27 wherein the nucleotide sequence to be the *trans*-spliced to the target pre-mRNA comprises a translational stop codon.

31. The nucleic acid molecule of claim 27 wherein the nucleotide sequence to be *trans*-spliced to the target pre-mRNA comprises nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator.

32. The nucleic acid molecule of claim 27 wherein the nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator comprise exons 1-10 cystic fibrosis transmembrane regulator gene.

33. A recombinant expression vector wherein said vector expresses a nucleotide sequence comprising:

- a) one or more target binding domains that target binding of the pre-*trans*-splicing molecule to a target pre-mRNA;
- b) a 5' splice donor site;
- c) a spacer region that separates the 5' splice donor site from the target binding domain; and
- d) a nucleotide sequence comprising the 5' end of a gene to be *trans*-spliced to the target pre-mRNA;

wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.

34. The molecule of claim 27 or 30 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the pre-*trans*-splicing molecule branch point, pyrimidine tract, or 3' splice site.

35. The recombinant expression vector of claim 33 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more

sides of the pre-*trans*-splicing molecule branch point, pyrimidine tract, or 3' splice site.

36. A cell comprising a nucleic acid molecule wherein said nucleic acid molecule comprises:

- a) one or more target binding domains that target binding of the pre-*trans*-splicing molecule to a target pre-mRNA;
- b) a 5' splice donor site;
- c) a spacer region that separates the 5' splice donor site from the target binding domain; and
- d) a nucleotide sequence comprising the 5' end of a gene to be *trans*-spliced to the target pre-mRNA;

wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.

37. The cell of claim 32 wherein the nucleic acid molecule further comprises sequences encoding a translatable protein product.

38. The cell of claim 36 wherein the nucleic acid molecule further comprises a nucleotide sequence containing a translational stop codon.

39. The cell of claim 36 wherein the nucleotide sequence to be *trans*-spliced to the target pre-mRNA comprises nucleotide sequences encoding the cystic fibrosis transmembrane regulator.

40. The cell of claim 39 wherein the nucleotide sequences encoding the cystic fibrosis trans-membrane regulator comprise exons 1-10 of the cystic fibrosis transmembrane regulator gene.

41. The cell of claim 37 wherein the translatable protein is a toxin.

42. A cell comprising a recombinant expression vector wherein said vector expresses a nucleotide sequence comprising:

- a) one or more target binding domains that target binding of the pre-*trans*-splicing molecule to a target pre-mRNA;
- b) a 5' splice donor site;
- c) a spacer region that separates the 5' splice donor site from the target binding domain; and
- d) a nucleotide sequence comprising the 5' end of a gene to be *trans*-spliced to the target pre-mRNA;

wherein said nucleic acid molecules is recognized by nuclear splicing components within the cell.

43. A cell comprising the nucleic acid molecule of claim 27 or 37 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the pre-*trans*-splicing molecule branchpoint, pyrimidine tract, or 5' splice site.

44. A cell comprising the recombinant expression vector of claim 33 further comprising a safety nucleotide sequence comprising one or more complementary sequences that bind to one or more sides of the pre-*trans*-splicing molecule branchpoint, pyrimidine tract, or 5' splice site.

45. A method of producing a chimeric mRNA molecule comprising contacting a pre-*trans*-splicing molecule with a target pre-mRNA under conditions in which a *trans*-splicing reaction results in a portion of the pre-*trans*-splicing molecule being *trans*-spliced to the 5' end of the target pre-mRNA to form said chimeric mRNA.

46. The method of claim 45 wherein the pre-*trans*-splicing mRNA comprises

nucleotide sequences encoding the cystic fibrosis transmembrane conductance regulator.

47. The method of claim 46 wherein the pre-*trans*-splicing mRNA comprises exons 1-10 of the cystic fibrosis transmembrane conductance regulator gene.

48. A method of providing a host cell with a chimeric mRNA molecule, said method comprising:

transferring a pre-*trans*-splicing molecule to a host cell expressing a target pre-mRNA wherein the pre-*trans*-splicing molecule binds to the target pre-mRNA under conditions in which a *trans*-splicing reaction results in a portion of the pre-*trans*-splicing molecule being *trans*-spliced to a 5' portion of the target pre-mRNA to form said chimeric mRNA.

49. The method of claim 48 wherein the host cell is a human cell.

50. The method of claim 48 wherein the pre-*trans*-splicing molecule comprises nucleotide sequences encoding a protein that is defective or lacking in the host cell.

51. The method of claim 50 wherein the pre-*trans*-splicing molecule comprises nucleotide sequences encoding a fragment of the cystic fibrosis transmembrane conductance regulator protein.

52. A pharmaceutical composition comprising the nucleic acid molecule of claim 27 and a pharmaceutically acceptable carrier.

53. A nucleic acid molecule wherein said nucleic acid molecule is CFTR PTM24.